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Design and synthesis of novel hydantoin-containing melanin-concentrating hormone receptor antagonists

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Abstract—We report here new chemical series acting as antagonists of melanin-concentrating hormone receptor 1 (MCHR-1). Synthesis and structure–activity relationships are described leading to the identification of compounds with optimized in vitro pharmacological and in vitro ADME profiles. In vivo activity has been demonstrated in animal models of food intake and depression.

Melanin-concentrating hormone (MCH) is a cyclic, 19-amino acid peptide, highly conserved in sequence among vertebrates. It is synthesized in cell bodies in the lateral hypothalamus and zona incerta of the central nervous system (CNS).[1] Considerable evidence suggests the involvement of MCH and one of its G-protein-coupled receptors (MCHR-1) in a variety of physiological processes such as the regulation of food intake and energy metabolism, stress and anxiety syndromes.[2] Intracerebroventricular (icv) administration and chronic infusions of MCH in rodents stimulate feeding behaviour and result in hyperphagia and obesity.[3,4] Transgenic mice overexpressing MCH show obesity and resistance to insulin.[5] In contrast, targeted disruption of the MCH gene in mice (*mch*−/−) results in a lean phenotype due to hypophagia and increased metabolic rate,[6] and MCHR-1 deficient mice (*mch1r*−/−) are lean with decreased fat mass.[7] In addition, central administration of MCH in rats induces anxiety,[8] and injection of MCH into the nucleus accumbens shell of rats increases their immobility in a forced swimming test (FST), suggesting enhanced depressive behaviour.[9] Therefore, pharmacological blockade at MCHR-1 appears as a promising approach for the treatment of obesity and several mood disorders.

Since the molecular characterization of MCHR-1 in 1999,[10] an important structural diversity of small molecular weight drug-like MCHR-1 antagonists has been produced.[11] Several MCHR-1 antagonists have been reported to induce hypophagia and weight loss in rodents after single or multiple ip and/or po administrations.[12] In addition, some MCHR-1 antagonists have been reported to produce effects similar to clinically used antidepressants and anxiolytics in different animal models of depression and anxiety.[13] Some MCHR-1 antagonists also demonstrated efficacy in rat models of urinary incontinence.[14] We report here novel hydantoin-containing chemical series, acting as MCHR-1 antagonists and significantly active in both rodent models of food intake and depression.

Many of the previously reported MCHR-1 antagonists, like those highlighted in Figure 1 (**1**,[15] **2**,[16] **3**[17] and **4**[18]), show closely related chemical structures suggesting a pharmacophore model where a hydrophobic moiety is linked to a basic amine through a hydrogen-bond acceptor linker (amide or urea) and a nonspecific spacer. Using the rhodopsin structure as a template of the transmembrane helical region of MCHR-1, the carbonyl present in the linker was proposed to be involved in a key interaction inside the MCHR-1 binding site, by forming a hydrogen bond with the side chain of Gln^{325} located on helix 6.[17] A presumed interaction

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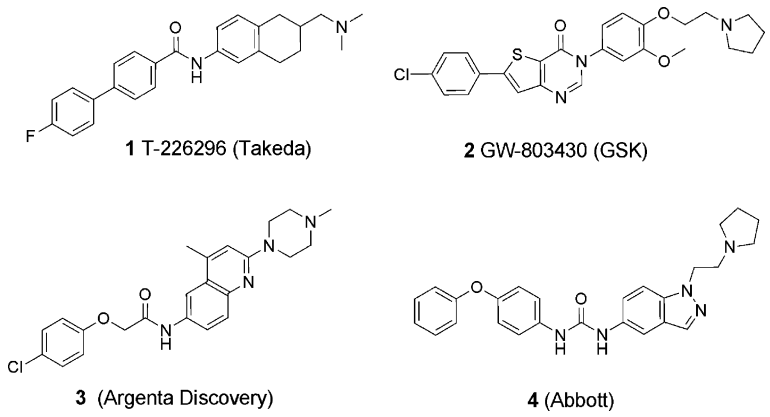
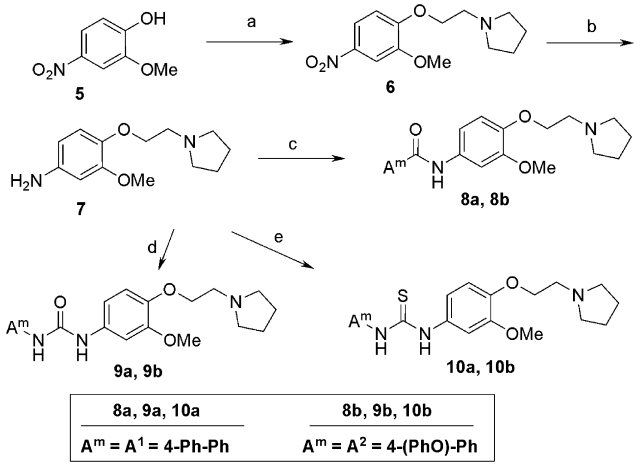


Figure 1. Examples of MCHR-1 antagonists.

between the basic amine and Asp[123] located in the third transmembrane domain of MCHR-1 was also reported.[19]

In order to identify new chemical series acting as MCHR-1 antagonists, different hydrogen-bond acceptor linkers were explored. According to the pharmacophore model mentioned above, the chemical structures of MCHR-1 antagonists drawn in Figure 1 were divided in three regions: the western hydrophobic region A, the central hydrogen bond acceptor region B and the eastern region C, gathering the nonspecific spacer and the basic amine. In a combinatorial approach, we designed several '$\mathbf{A}^m$–$\mathbf{B}^n$–$\mathbf{C}^p$' molecules by coupling two hydrophobic western parts (biphenyl $\mathbf{A}^1$ and 4-phenoxyphenyl $\mathbf{A}^2$) to different hydrogen-bond acceptor linkers and the eastern part $\mathbf{C}^1$ of compound **2** (Fig. 2).

The methods followed to prepare the different '$\mathbf{A}^1$–$\mathbf{B}^n$–$\mathbf{C}^1$' and '$\mathbf{A}^2$–$\mathbf{B}^n$–$\mathbf{C}^1$' molecules where $\mathbf{B}^n$ is either an amide ($\mathbf{B}^1$), urea ($\mathbf{B}^2$), thiourea ($\mathbf{B}^3$), 1-amino-thiazole ($\mathbf{B}^4$) or hydantoin ring ($\mathbf{B}^5$ and $\mathbf{B}^6$) linker are outlined below (Schemes 1–4). The target compounds **8a**, **8b**, **9a**, **9b**, **10a** and **10b** were prepared by the route described in Scheme 1: 1-chloro-2-*N*-pyrrolidinyl-ethane reacted with 4-nitro-2-methoxyguiacol to form ether **6**. Reduction of this material by catalytic hydrogenation over palladium/carbon in ethanol at room temperature and atmospheric pressure afforded aniline **7**. This key intermediate was used to form amides **8a** and **8b** by reaction with the corresponding acyl chlorides in dichloromethane in the presence of triethylamine, or by reaction with the corresponding carboxylic acids using TBTU in DMF. Aniline



Scheme 1. Reagents and conditions: (a) 1-Pyrrolidinyl-CH_2CH_2Cl·HCl, K_2CO_3, H_2O, DMF, 80 °C (81%); (b) H_2, 10% Pd/C, EtOH, rt, 1 atm (95%); (c) $\mathbf{A}^m$COCl, CH_2Cl_2, NEt_3, rt or $\mathbf{A}^m CO_2H$, TBTU, HOBT, DMF, rt (82–95%); (d) $\mathbf{A}^m$–NH_2, CDI, THF, rt (75–87%); (e) $\mathbf{A}^m$–NH_2, ThioCDI, THF, rt (77–85%).

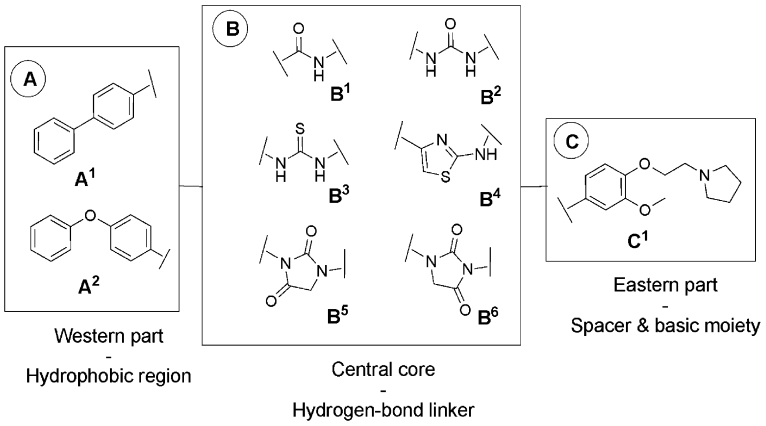
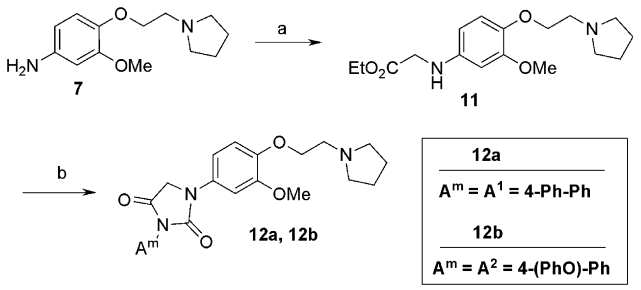
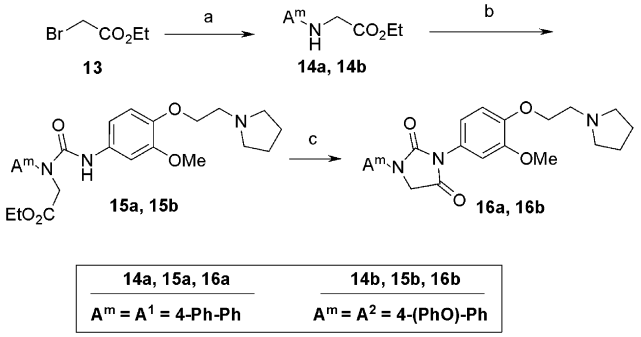


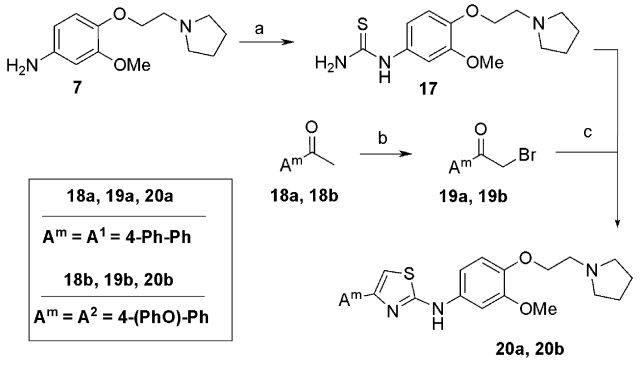
Figure 2. Combinatorial approach to identify new MCHR-1 antagonists.



Scheme 2. Reagents and conditions: (a) Ethyl-glyoxolate (50% in toluene), Na_2SO_4,, 1,2 dichloroethane, 60 °C, 16 h, then H_2, 10% Pd/C, EtOH, rt, 1 atm (70%); $\mathbf{A}^m$–NCO, CH_2Cl_2, TEA (39–52%).



Scheme 3. Reagents and conditions: (a) $\mathbf{A}^m$–NH_2, K_2CO_3, CH_3CN, 80 °C (67–79%); (b) **7**, CDI, THF, rt (75–87%); (c) EtONa, EtOH (57–74%).



Scheme 4. Reagents and conditions: (a) ThioCDI, NH_3 gas, CH_2Cl_2, rt (85%); (b) Br_2, Et_2O (83–90%); (c) EtOH, reflux (65–82%).

7 was also converted into urea **9a** and **9b** and thiourea **10a** and **10b** by reaction with the corresponding aniline $\mathbf{A}^m$–NH_2 directly using carbonyldiimidazole or thiocarbonyl-diimidazole in THF.

Hydantoin analogues **13a** and **13b** were prepared in three steps from aniline **7** (Scheme 2). The latter reacted with ethyl 2-bromo-acetate to form α-amino-ester intermediate **11**. This material was added to the corresponding isocyanates $\mathbf{A}^m$–NCO to give compounds **12a** and **12b**.

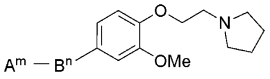
Similarly, hydantoin analogues **16a** and **16b** were prepared in three steps starting from the corresponding anilines $\mathbf{A}^m$–NH_2 (Scheme 3). α-Amino-esters **14a** and **14b** were prepared by nucleophilic displacement of ethyl 2-bromo-acetate **13** in the presence of potassium carbonate in acetonitrile. These intermediates were further converted into ureas **15a** and **15b** by reaction with aniline **7** in the presence of carbonyldiimidazole in THF. Cyclization was then conducted in the presence of sodium ethoxide in ethanol to yield compounds **16a** and **16b**.

Compounds **20a** and **20b** were prepared in three steps from aniline **7** and the two methyl-ketones $\mathbf{A}^m$–$COCH_3$ **18a** and **18b** (Scheme 4). First, thiourea **17** was prepared from aniline **7** and thiocarbonylimidazole by condensing ammonia. Bromination of methyl-ketones **18a** and **18b** was performed with bromine in diethyl ether to give α-bromo-methyl-ketones **19a** and **19b**. These intermediates reacted with thiourea **17** to afford the expected compounds **20a** and **20b**, respectively.

The different '$\mathbf{A}^m$–$\mathbf{B}^n$–$\mathbf{C}^1$' molecules were then evaluated for binding to the MCHR-1 and compared to compound **1** (Table 1). Amide analogues **8a** and **8b** appeared to be the most potent compounds (K_i < 100 nM) when compared with compound **1** (38 nM). Interestingly, compound **12b** showed, for MCHR-1, a moderate affinity (K_i = 164 nM), but a good selectivity (K_i for MCHR-2 > 10 μM). In addition, antagonism behaviour of **12b** was demonstrated in a MCH mediated calcium release assay in recombinant CHO cells stably expressing human MCHR-1. The specificity profile of **12b** was assessed by analyzing the binding of the compound to a panel of 75 receptors, ion channels and transporters.[20] Profile analysis demonstrated that **12b** displayed a significant affinity for the 5-HT2a receptor (K_i = 330 nM), the 5-HT2c receptor (K_i = 880 nM) and the muscarinic M4 receptor (K_i = 370 nM).

We hypothesized that the eastern region $\mathbf{C}^1$ of compound **12b** ($\mathbf{A}^2$–$\mathbf{B}^5$–$\mathbf{C}^1$ molecule) was primarily responsible for its high affinity for serotonin receptors. New hydantoin analogues ($\mathbf{A}^2$–$\mathbf{B}^5$–$\mathbf{C}^p$ molecules) were designed and screened in silico onto predictive binding

Table 1. Affinities of '$\mathbf{A}^m$–$\mathbf{B}^n$–$\mathbf{C}^1$' molecules for MCH-R1[a]



Compound	$\mathbf{A}^m$	$\mathbf{B}^n$	MCH-R1 K_i[b] (nM)
1	—	—	38
8a	$\mathbf{A}^1$	$\mathbf{B}^1$	25
8b	$\mathbf{A}^2$	$\mathbf{B}^1$	82
9a	$\mathbf{A}^1$	$\mathbf{B}^2$	260
9b	$\mathbf{A}^2$	$\mathbf{B}^2$	101
10b	$\mathbf{A}^2$	$\mathbf{B}^3$	1090
12a	$\mathbf{A}^1$	$\mathbf{B}^5$	415
12b	$\mathbf{A}^2$	$\mathbf{B}^5$	164
16a	$\mathbf{A}^1$	$\mathbf{B}^6$	>5000
16b	$\mathbf{A}^2$	$\mathbf{B}^6$	365
20b	$\mathbf{A}^2$	$\mathbf{B}^4$	1000

[a] All compounds were >95% pure by HPLC and characterized by ^1H NMR and LCMS. All values are mean values ± SEM ($n \geqslant 2$).

[b] Displacement of [^{125}I][Phe^{13}, Tyr^{19}]-MCH from human recombinant MCHR-1 expressed in CHO cells (Kd = 1 nm).

models towards 5-HT2a and 5-HT2c receptors. Benzylidene derivative **21** was identified as a promising virtual hit built on a more constrained scaffold.

Figure 3 reports overlays of two conformations of compound **12b** and compound **21** suggesting that the basic amine (pyrrodinyl group) should fit into the same region inside MCHR-1 binding site.

Compound **21** was prepared in five steps from ethyl isocyanatoacetate **22** (Scheme 5). The latter reacted with 4-phenoxy-aniline to form urea **23** which can be further transformed into hydantoin **24** under alkaline conditions. 4-Diethoxyethylbenzaldehyde could react with compound **24** under Knoevenagel conditions to give benzylidene intermediate **25**. Interestingly, only the formation of the *Z*-isomer was observed as evidenced by NMR. The ^{1}H NMR chemical shifts of the *N*-methyl analogue of **25**, formed by stirring the latter with methyl iodide under alkaline conditions, were compared to its *E*-diastereoisomer prepared directly from 1-(4-phenoxy-phenyl)-3-methyl-hydantoin under similar Knoevenagel conditions.[21] Hydrolysis of the diethylacetal group of **25** gave the corresponding aldehyde which could be converted into compound **21** by reacting with pyrrolidine in the presence of a reductive agent such as triacetoxyborohydride.

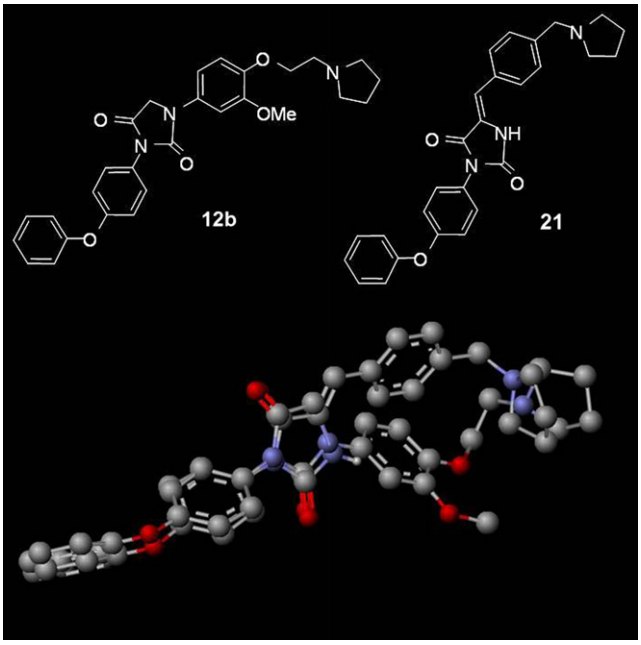
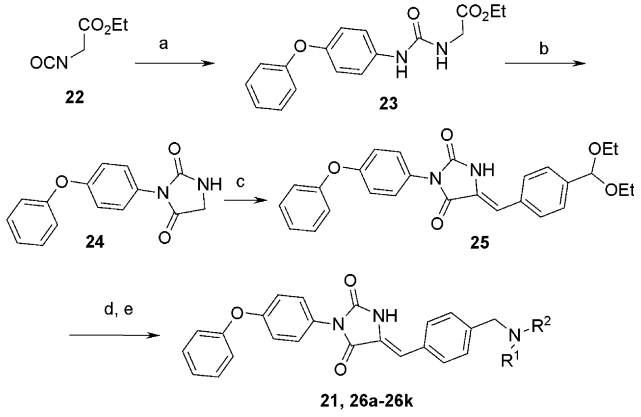


Figure 3. Conformation overlays of compound **12b** and compound **21**.



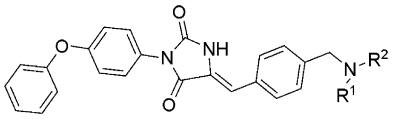
Scheme 5. Reagents and conditions: (a) 4-phenoxy-aniline, CH_2Cl_2, rt (94%); (b) NaOH, EtOH, rt overnight, then HCl concd, H_2O, reflux (93%); (c) 4-diethoxymethylbenzaldehyde, EtOH, $MgSO_4$, pyrrolidine (46%); (d) HCl (1 N), 2 h, 50 °C (92%); (e) NHR^1R^2, Na_2SO_4, $BH(OAc)_3$, CH_2Cl_2, rt, overnight (3–68%).

Compound **21** was evaluated for binding to MCHR-1, MCHR-2 and to the same panel of 75 pharmacological targets. Compound **21** showed a high selectivity for MCHR-1 versus MCHR-2 (K_i for MCHR-1 = 220 nm; K_i for MCHR-2 > 10 μM) (Table 2). Only low affinity was observed for serotonin receptors 5-HT2a (K_i > 5 μM) and 5-HT2c (K_i > 10 μM). In fact, no significant activity (K_i < 500 nm) was found except for Ca^{2+} channel, L-verapamil site (330 nm). Antagonism behaviour of **21** was also demonstrated in a MCH mediated calcium release assay. In addition, compound **21** showed a drug-like in vitro ADME profile, particularly a good Caco-2 permeability (>60 nm/s) predicting a significant absorption after oral administration.

Based on the improvements of the selectivity against off-target receptors, a series of benzylidine derivatives was prepared to potentially elicit improved affinity for MCHR-1. Starting from compound **25**, reductive amination reactions were performed using 11 different amines (Scheme 5). Compound **26k** obtained from (+/−)-3-hydroxypyrrolidine showed the best affinity (K_i = 176 nm) (Table 2).

In order to establish the therapeutic potential of these series of MCHR-1 antagonists, the effects of compounds

Table 2. Structure–activity relationship found on the series of benzylidene derivatives built around compound **21**[a]



Compound	NHR^1R^2	MCH-R1 K_i[b] (nM)
21	Pyrrolidine	220
26a	Cyclopentylamine	>5000
26b	Benzylamine	>5000
26c	Dimethylamine	341
26d	Piperidine	>5000
26e	Hexahydroazepine	357
26f	Morpholine	>5000
26g	2-Dimethylaminoethylamine	707
26h	4-Acetyl-piperazine	2060
26i	4-Phenyl-piperazine	>5000
26j	4-Benzyl-piperazine	>5000
26k	(+/−) 3-Hydroxypyrrolidine	176

[a] See Table 1, footnote a.
[b] See Table 1, footnote b.

12b, **21** and **26k** on food intake were assessed in overnight fasted mice and compared to the anti-obesity drug, sibutramine (Meridia®) (Fig. 4). All compounds tested induced a significant reduction of food intake after acute ip administrations at 30 mg/kg. Cumulative food intake was, respectively, reduced by 51%, 41% and 47% relative to vehicle controls, 3 h after injection of compounds **12b**, **21** and **26k**. In addition, antidepressant potential of compound **21** was assessed in a forced swimming test in mice. When compared to control animals treated by vehicle, immobility duration measured 30 min after administration of compound **21** (30 mg/kg, ip) was significantly reduced. Indeed, in vivo effects of compound **21** (−57%) were comparable to the effect of a clinically used antidepressant, imipramine (10 mg/kg ip; −58%).

Finally, acute toxicity of compound **21** and its effects on general activity and behaviour were assessed based on a modified Irwin's method in mice.[22] Compound **21** was given intraperitoneally to mice at 10, 30 and 100 mg/kg and comparisons were made with a vehicle control group. No major side effect could be observed while slight and transient prostration was noted within the first 5 min after injection of the highest doses. However, potential risk of cardiac side-effects associated with compound **21** was highlighted in a standard in vitro electrophysiology assay on hERG K^+ channel. When tested at 1 μM, compound **21** induced a 73% current amplitude inhibition.

In summary, we were able to design and to synthesize a novel series of hydantoin-containing compounds, and evaluate their potency as antagonists of MCHR-1. SAR analysis showed that some compounds exhibited activities below 200 nm. A rational chemical optimization work was conducted to reduce off-target affinities in order to minimize unexpected side-effects. This work allowed the identification of compound **21**, a lead molecule significantly active in both rodent models of food intake and depression. Further medicinal chemistry efforts still remain to be done to improve the hERG selectivity of this novel chemical series.

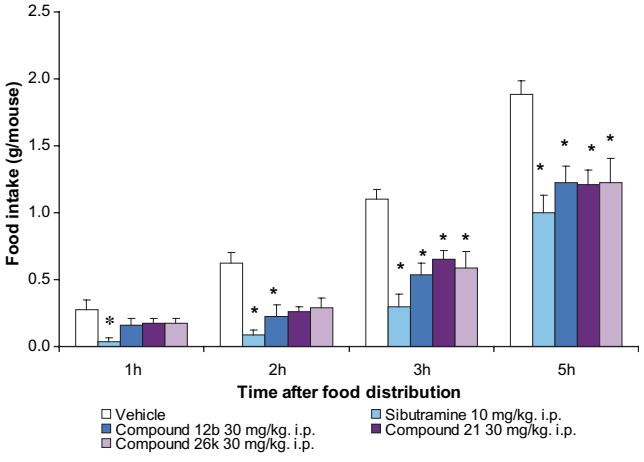


Figure 4. Effects of Sibutramine (10 mg/kg, ip), compound **12b** (30 mg/kg, ip), compound **21** (30 mg/kg, ip) and compound **26k** (30 mg/kg, ip) on cumulative food intake in overnight fasted mice. Results are expressed as means + SEM ($n = 8$ male OF1 mice per group). *Indicates significant difference versus vehicle group-treated for $P < 0.05$ (Dunett's method).

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